Remarks

This is a response to the Office Action mailed January 17, 2003. Presently, claims 1, 2, 5-11 and 19-29 are pending and have been rejected. Claims 1, 5, 8, 20, 21, 22, 23, 24, 25, 26, 27, 28, and 29 are currently amended.

Objection to disclosure. The Office Action states that the amendments to the specification need to be re-submitted in proper format. Applicants have resubmitted the amendments with the submission of the entire paragraphs.

Objection to the claims. The Office Action states that claims 5, 8, 20, 21 and 24-27 are objected because of a series of informalities in spelling and punctuation. Claims 5, 8, 20, 21 and 24-27 have been amended to correct said informalities.

Rejection under 35 U.S.C.§ 112, first paragraph.

The Office Action states that claims 1, 2, 5, 7-11 and 19-29 are rejected under 35 U.S.C.§ 112, first paragraph as containing subject matter that was not described in the specification in a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention. The Office Action states that there is no disclosure supporting the claim limitation requiring HIV protease inhibitors – other than ABT-538 – to be in the amorphous form. Applicants respectfully disagree. Example 1.A. describes the dispersion preparation for ABT-538. The description states that ABT-538 is dissolved in ethanol in a flask and then mixed with PEG 8000, continuously mixing until PEG melted. "...The flask was then attached to a rotary evaporator, immersed in the water bath at 75° C under vacuum for 15 minutes to remove the ethanol. After the majority of the ethanol had evaporated, the flask was immersed in an ice bath for 15 minutes"... (page 14 lines 15-19 of the present specification). This evaporation of ethanol at a high temperature and for a short period of time is considered by those skilled in the art to be a rapid evaporation, which, as known in the art, will lead to the formation of the amorphous form of the dissolved drug, in this case ABT-538. This is supported also by the title of figures 1 and 2, which state in that ABT-538 is indeed in amorphous form. Because Example

1.B describes the dispersion preparation of ABT-378 to be performed according to the same procedure as described in Example 1.A., Applicants consider that this is enough description to convey the message that ABT-378 is also in amorphous form. Similarly, Example 1.C., describes the dispersion preparation of nelfinavir to be performed according to the same procedure as described in Example 1.A., Applicants consider that this is enough description to convey the message that nelfinavir is also in amorphous form.

The Office Action also states that new claims .22-29 are drawn to dispersions in general, rather than solid dispersions. Claims 22-29 have been amended to indicate solid dispersions.

Rejections under 35 U.S.C. § 102(b).

Claims 1, 2, 5 and 11 are rejected under 35 U.S.C. § 102(b) as being anticipated by Aungst *et al* (Int. J. Pharmaceutics, Vol 156, pages 79-88). Applicants respectfully disagree. The legal standard for anticipation is that a claim is anticipated only when a single prior art reference discloses each and every limitation in the claim. Claim 1, as amended, claims pharmaceutical compositions comprising a solid dispersion of an HIV protease inhibitor or a combination of HIV protease inhibitors in a water soluble carrier wherein said water soluble carrier is polyethylene glycol 8000 (PEG 8000) and wherein the HIV protease inhibitor or the combination of HIV protease inhibitors is in amorphous form in the dispersion, and in claim 5, wherein the HIV protease inhibitor is selected form the group consisting of ritonavir, ABT-378, indinavir, saquinavir, 5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide; 1 -Naphthoxyacetyl-beta-methylthio-Ala-(2S, 3S)-3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4- t-butylamide; 5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide; [1S-[1R-(R-), 2S*])-N^1-[3-[[[(1,1 -dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1 -(phenylmethyl)propyl] -2-[(2quinolinylcarbonyl)amino]-butanediamide; VX-478; DMP-323; DMP-450; AG1343 (nelfinavir); BMS 186,318; SC-55389a; BILA 1096 BS; and U-140690.

Aungst *et al* teaches formulations using the HIV protease inhibitor DMP323 dissolved in several combinations of PEG 400 or PEG 3350, with polysorbate, ethanol, Na laurylsulfate, etc. as described in Table 2. Additionally, Aungst *et al* does not teach the evaporation procedure under which the solvents are evaporated, therefore the assumption that DMP323 is in amorphous form does not have a foundation. Applicants submit that Aungst *et al* does not disclose each and every limitation of claims 1, 5 and 11 of the present application. Applicants are not clear how the Examiner is expecting Applicants to provide evidence that the claimed solid dispersions are unobviously different than those of Aungst *et al* when the claims are rejected under § 102(b).

The Office Action states that Claims 1, 2, 5, 9, and 11 are rejected under 35 U.S.C. § 102(b) as being anticipated by Aungst *et al* (B.T. Gattetosse, Vol. 87, pages 49-54). Applicants respectfully disagree. Aungst *et al* teaches formulations of DMP323 in PEG 3350 alone or in combination with Na lauryl sulfate or PVP 40000. Additionally, the solvent used is a mixture of ethanol and methylene chloride without any description as to how the process of evaporation is conducted, therefore the assumption that DMP323 is in amorphous form does not have a foundation. Claims 1, 5, and 11, as amended, claim formulations of HIV protease inhibitors in PEG 8000 dissolved in pure ethanol, wherein the HIV protease inhibitors are in amorphous form. Therefore, Applicants submit that Aungst *et al* does not disclose each and every limitation of claims 1, 5 and 11 of the present application. Applicants are not clear how the Examiner is expecting Applicants to provide evidence that the claimed solid dispersions are unobviously different than those of Aungst *et al* when these claims are rejected under § 102(b).

Claims 1, 2, 5, 6, 9, 11, 19, 20, 22, and 23 are rejected under 35 U.S.C. § 102(b) as being anticipated by Al-Razzak *et al.* (US Patent No. 5,610,193). Applicants respectfully disagree with this assertion. Al-Razzak *et al* claims pharmaceutical compositions comprising adsorbent or mixtures thereof, an organic solvent or mixtures thereof, a HIV protease inhibitor, and a pharmaceutically acceptable acid or combinations thereof. Applicants consider of paramount importance that the Examiner recognizes that the formulation of Al-Razzak *et al* has an improved solubility and bioavailability due to the addition of acids, i.e., the HIV protease inhibitor are made into salts, and therefore made more soluble, independently of the organic solvents used (column 3, lines 45-55).

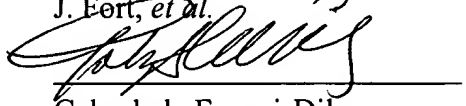
The present application describes a formulation of HIV protease inhibitor that are in the amorphous form, and therefore more soluble. The fact that the formulations of Al-Razzak *et al* do not comprise HIV protease inhibitor in amorphous form can be deduced from the process of making the formulations. The formulation granulation of Al-Razzak *et al* is tray dried at low temperature (20° C -35° C), i.e. very slow evaporation process to remove the ethanol if used as a cosolvent (column 9 lines 58-63, column 12, lines 33-36). The evaporation process of the formulations of the present application consists of rapid evaporation of ethanol (75° C under vacuum for 15 minutes) resulting in the amorphous physical form of the HIV protease inhibitor (Example 1.A. of the description).

Applicants acknowledge withdrawal of the rejections under 35 U.S.C. § 103(a).

Conclusion

Applicants believe to have properly addressed all of Examiner's objections and rejections with the amendments and remarks in the present reply. Applicants respectfully request reconsideration and allowance of the claims presently pending. If the Examiner believes that allowance may be expedited by a telephone interview, the Examiner is respectfully requested to contact the undersigned.

Respectfully submitted,
J. Fort, *et al.*



23492
ABBOTT LABORATORIES
Abbott Park, Illinois 60064-6008
Phone: (847) 935-4314
FAX: (847) 938-2623

Gabryleda Ferrari-Dileo
Registration No. 55,174
Attorney for Applicants